

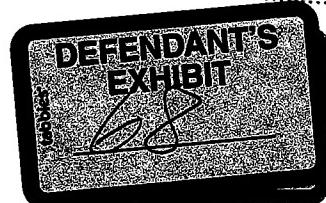
# **EXHIBIT 68**

**Establishment Inspection Report**  
 Actavis Totowa LLC  
 Little Falls, NJ 07424-5608

FEI: 2244683  
 EI Start: 09/05/2007  
 EI End: 09/28/2007

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**SUMMARY**

This inspection of a pharmaceutical manufacturer was conducted as a follow-up to Warning Letter # 07-NWJ-06 and was completed as part of the NWJ-DO FY07 Drug Work Plan under FACTS Assignment # 4041339, Operation ID # 3240435. The inspection provided general GMP coverage as well as pre-approval coverage of [REDACTED]

[REDACTED] Inspectational guidance was afforded through Compliance Program Guidance Manuals 7356.002: Drug Manufacturing Inspection and 7346.832: Pre-Approval Inspections/Investigations.

The previous GMP inspection of 7/10/2006 et. al., provided coverage to the Quality, Production, Laboratory Control and Materials Systems. Limited coverage was also provided to the Facilities & Equipment System as necessary, but this system was not covered in its entirety. An FDA 483, Inspectational Observations, was issued at the closeout meeting regarding deficiencies in the areas of Quality Control, laboratory records, OOS and production investigations, cleaning validation, bulk stability testing, detection and documentation of OOS results, sampling documentation, equipment qualification, calibrations and preventive maintenance, rejected materials and storage of components. In addition, a discussion was held with management regarding the labeling of laboratory glassware and stability of solutions. Corrections were promised for all observations and discussion items. The inspection was classified OAI for GMP deficiencies and Warning Letter # 07-NWJ-06 was issued.

The Quality, Production, Laboratory Control, Materials and Facilities & Equipment Systems were covered during the current inspection and corrections made since the previous inspection were verified. An FDA 483, Inspectational Observations, was issued at the closeout meeting regarding deficiencies in the areas of Field Alerts, the stability testing program, and investigations. In addition, a discussion was held with management regarding additional items not listed on the FDA 483. Corrections were promised for all observations and discussion items. An approval recommendation was submitted for ANDA 40830/000 Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Capsules 356.4 mg / 30 mg / 16 mg upon completion of the inspection. Corrections to the previous PADE inspection will be verified under the next assignment for the Elizabeth facility as all ADE operations have been transferred to that facility since the previous inspection.

**ADMINISTRATIVE DATA**

Inspected firm: Actavis Totowa LLC  
 Location: 101 E Main St  
 Little Falls, NJ 07424-5608

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Phone: 973-890-1440  
FAX:  
Mailing address: 101 E Main St  
Little Falls, NJ 07424-5608

Dates of inspection: 9/5/2007, 9/6/2007, 9/10/2007, 9/11/2007, 9/12/2007, 9/13/2007,  
9/14/2007, 9/18/2007, 9/20/2007, 9/21/2007, 9/24/2007, 9/25/2007,  
9/26/2007, 9/27/2007, 9/28/2007

Days in the facility: 15  
Participants: Kristy A. Zielny, Investigator

On 9/5/07, I, Investigator Kristy A. Zielny, presented my credentials and issued an FDA 482, Notice of Inspection, to Mr. Apurva Patel, Managing Director. Mr. Patel stated he was authorized to receive the Notice. A "Resources for FDA Regulated Businesses" form was also presented at this time. I explained that the purpose of my visit was to provide follow-up coverage to Warning Letter # 07-NWJ-06, pre-approval inspectional coverage to [REDACTED] as well as GMP inspectional coverage. Mr. Jasmine Shah, Vice President, Regulatory and Medical Affairs, was also present for the initiation of the inspection. Mr. Scott Talbot, Site Head of Quality joined the inspection later that morning.

Mr. Scott Talbot provided all requested information and documentation as requested and arranged meetings with additional personnel as necessary. A facility tour was also provided.

[REDACTED]  
[REDACTED] was collected at the close of this inspection.

On 9/28/07, an FDA 483, Inspectional Observations, was issued to Mr. Apurva Patel, Managing Director. In addition, a discussion was held with management both during the inspection and again at the closeout meeting. Corrections were promised for all observations and discussion items. A written response to the 483 observations was promised as well.

[REDACTED]  
[REDACTED] the close of this inspection.

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FEI:	<b>2244683</b>
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**HISTORY**

Actavis Totowa LLC currently consists of three sites. This site, located at 101 East Main Street, Little Falls, NJ, is responsible for all manufacturing and testing as well as raw material receiving. The second site is located at 4 Taft Road, Totowa, NJ, and is responsible for all packaging, labeling, distribution, packaging component receiving and R&D. Some overflow testing is also completed at the Taft Road Facility as well as the testing of ANDA submission batches. Actavis Totowa LLC is in the process of moving its operations from the Little Falls facility to a third site, located at 900 Riverview Drive, Totowa, NJ. The Riverview facility is listed under the same FEI # as the Little Falls site and is currently being used for storage and office space. Laboratory equipment has already been transferred to the Riverview site and the Quality Control Laboratory is expected to initiate testing any day. All operations currently at the Little Falls facility are expected to be fully transferred to the Riverview site. The Riverview facility was visited as part of the current inspection.

This site, previously operating as Amide Pharmaceutical, Inc. was founded in 1983 and was acquired by Actavis on July 27, 2005. The name legally changed to Actavis Totowa LLC on May 15, 2006. Actavis Totowa LLC is a wholly owned subsidiary of Actavis Group, which was founded in 1956 and is based in Reykjavick, Iceland.

All regulatory correspondence should be addressed to Mr. Apurva Patel, Managing Director of Actavis Totowa LLC, at 101 East Main Street, Little Falls, NJ 07424. Mr. Apurva Patel is the most responsible individual at this facility, which is also the current headquarters for Actavis Totowa LLC. Mr. Divya Patel, President of Actavis U.S. Operations should also be copied on all correspondence at 900 Riverview Drive, Totowa, NJ.

This facility currently operates 7:30 AM through 4:00 PM, Monday through Friday, and as needed on weekends. There are approximately [REDACTED] individuals employed at this facility. This site consists of two buildings: Building A is [REDACTED] square feet and consists of administration, manufacturing, QA, QC, RA, and warehouse. Building B is approximately [REDACTED] square feet and is being decommissioned but is still used for some warehousing operations. The floor plan of the manufacturing facility at Little Falls is attached as Exhibit 1. The Riverview facility, where operations are slated to be transferred, consists of nearly twice as much space with [REDACTED] square [REDACTED] of which will be manufacturing space.

Major customers include [REDACTED]

The annual volume of sale for Actavis Totowa LLC, was approximately \$160 million in 2006.

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**COMPLIANCE STATUS**

A Warning Letter was issued to Actavis Totowa LLC, Little Falls, as a result of the previous inspection. The firm has been operating under a Compliance Hold since the receipt of Warning Letter # 07-NWJ-06.

A second Warning Letter was issued to Actavis Totowa LLC, Little Falls, on 2/26/07 for the manufacturing of DESI products. The production of all of these products has been discontinued.

**INTERSTATE COMMERCE**

Mr. Scott Talbot provided an estimation of interstate commerce at approximately 85 to 90%. Products that are manufactured at 101 East Main Street, Little Falls, are packaged, labeled at the 4 Taft Road, Totowa facility before being sent to UPS for distribution. All products are sent to UPS Louisville located at 1860 Outerloop, Louisville, KY 40219, with the exception of controlled substances, which are sent to UPS Newark, 222 Lake Drive, Newark, DE 19702. The Central Distribution Center is no longer being used for distribution functions.

**JURISDICTION**

Actavis Totowa LLC is a large generic pharmaceutical manufacturer. The Little Falls facility is responsible for raw material receiving, all manufacturing and testing of drug products. Dosage forms manufactured at this facility include prompt release tablets and capsules and extended release tablets. A complete list of products manufactured at the Little Falls facility was provided and is attached as Exhibit 2.

**INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED**

Mr. Scott Talbot accompanied me throughout the inspection and arranged for meetings with additional individuals as necessary. Individuals who provided information throughout the inspection include the following:

Scott Talbot, Site Head of Quality —

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Apurva Patel, Director, Site Operations  
Phyllis Lambridis, VP, Quality Compliance for Actavis U.S.  
Jasmine Shah, VP, Regulatory and Medical Affairs for Actavis, U.S.  
Wanda Eng, Sr. Director Corporate Compliance for Actavis U.S.  
Daniel Bitler, Director, QA Director – Little Falls  
Richard Dowling, Director, Manufacturing Operations  
Garret Wolan, Compliance Manager for Actavis U.S.  
Nilesh Patel, QC Instrument & Metrology Manager  
Elina Novikov, QC Laboratory Compliance Manager  
Gaurang Pandya, Group Leader, Analytical Research  
Katherine Chuang, Project Manager  
Vince D'Esposito, Training Manager  
Bernard Glover, QA Specialist

The following are the key officials of Actavis Totowa LLC:

**Mr. Apurva Patel, Director, Site Operations**

Mr. Patel is responsible for leading all site activities and is accountable for Manufacturing, Health & Safety, Release, Engineering and Maintenance. Mr. Patel reports to Mr. Steinholt Palsson, EVP Operation, Management Board, who, in turn reports directly to Mr. Robert Wessman, CEO.

**Mr. Scott Talbot, Site Head of Quality**

Mr. Talbot is responsible for the assurance of quality within Actavis Totowa, LLC. He is responsible for all Quality Systems as they relate to the development, manufacturing testing and distribution of pharmaceutical products under GMPs. Mr. Talbot reports to Mr. Divya Patel, Executive Chairman, Management Board, who, in turn reports directly to Mr. Robert Wessman, CEO.

**Mr. Daniel Bitler, QA Director – Little Falls**

Mr. Bitler is responsible for the assurance of quality within the Little Falls sites. He is responsible for all Quality Systems as they relate to the manufacturing and distribution of pharmaceutical products manufactured at the Little Falls facilities.

**Mr. Swapan Roychowdhury, Quality Control Director**

Mr. Roychowdhury is responsible for all Quality Control functions. He is responsible for all testing of all raw materials and finished products as well as the training of analysts, the evaluation of data and the assurance that all instruments are qualified, calibrated and maintained.

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Mr. Anthony Castellazzo, QS Director – Totowa

Mr. Castellazzo is responsible for the assurance of quality within the Totowa sites. He is responsible for Validation, Technology Transfer and the packaging and distribution of pharmaceutical products from the Totowa sites. He is also responsible for assuring all equipment, facilities, utilities and processes are validated.

Mr. Paul Galea, QS Director

Mr. Galea is responsible for all Internal Audits, Complaints, Change Control, CAPA and Training.

Mr. Harish Vakil, Validation Associate Director

Mr. Vakil is responsible for the validation of all facilities, utilities, equipment, processes and cleaning related to the manufacturing, packaging, and distribution of pharmaceutical products.

Mr. Richard Dowling, Director of Manufacturing Operations

Mr. Dowling is responsible for all manufacturing operations related to all Actavis Totowa LLC products.

Mr. Bharat Patel, Vice President, Materials Management

Mr. Bharat Patel is responsible for all purchasing for the Actavis Totowa facilities as well as production planning and managing inventory.

Organizational charts and Position Descriptions were provided and are attached as **Exhibits 3 and 4**, respectively.

The most responsible individual at this site is Mr. Apurva Patel, Director, Site Operations. All regulatory correspondence should be addressed to his attention at 101 East Main Street, Little Falls, NJ 07424.

**CHANGES IN OPERATIONS AND PERSONNEL**

The following changes in personnel have taken place since the previous inspection of January 2006. Mr. Apurva Patel, previously Director, Project Management, became Site Head of Operations as of June 2007.

Mr. Scott Talbot, Site Head of Quality, came to Actavis Totowa LLC as of 1/9/07.

Mr. Anthony Castellazzo became Director, Quality Assurance – Totowa as of July 2007

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Mr. Swapan Roychowdhury became Director, Quality Control as of April 2007.

Mr. Harish Vakil, Acting Director, Validation came to Little Falls as of May 2007.

Mr. Paul Galea became Director, Quality Systems as of May 2007.

Mr. Steinthor Palsson, previously Site head of Operations, Malta, became Executive VP, Operations as of August 2006.

Mr. Divya Patel, previously President and CEO of Actavis Totowa LLC, became Executive Chairman as of April 2007.

Mr. Jasmine Shah, previously VP, Regulatory and Quality Compliance; became VP, Regulatory and Medical Affairs as of January 2007.

Ms. Phylis Lambridis, joined Actavis as Vice President of Quality and Compliance, U.S. in September 2007.

A number of additional individuals have been hired and/or have been promoted since the previous inspection, including, but not limited to:

Vince D'Esposito, Training Manager  
Jisheng Zhu, Quality Control Manager  
Elina Novikov, Stability Manager  
Chrystal Day, Stability Coordinator  
Joaquin Mejia, Stability Coordinator  
Bernard Glover, CAPA and Complaints Specialist  
Mike Ponzo, Investigation Specialist  
Elizabeth Guarch, Validation Manager  
Irina Kotkova, Validation Specialist  
Lauren Miranda, Quality specialist  
Pam Barckett, Documentation Specialist

In addition, four new analysts and two temps have been brought into the QC Laboratory. An additional two analysts were hired during the course of the inspection.

The following changes have been made in operations since the previous inspection:

A number of products have been discontinues since the previous inspection. Some of these products include, but are not limited to: Isoxsuprine Hydrochloride Tablets, USP 10 mg and 20 mg, Dexchlorpheniramine Maleate Tablets (Time Released) 4 mg and 6 mg, Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules, Amagesic (Salsalate Tablets 500 mg and 750 mg, Amadrine Capsules, Choline Magnesium Trisalicylate Tablets 500 mg, 750 mg, 1000 mg, AmiTex PSE Tablets, Hyoscyamine Sulfate Tablets 0.125 mg. A list of discontinued products was provided and is attached as Exhibit 5.

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The reporting of Adverse Drug Events has been moved to the Elizabeth facility as of April 2006.

The Quality Systems Improvement Plan (QSIP) was initiated as of August 29, 2006. QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAPA, Documentation, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance/Audits, Warehouse/Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. A copy of the plan was provided and is attached as Exhibit 6. Consultants were utilized beginning in September 2006 in order to assess key areas.

All Standard Operating Procedures (SOPs) and Departmental Operating Instructions (DOIs) have been reviewed and uploaded into QMAS, a validated computer system, which will enable employees to access all procedures and instructions on-line and will ensure that only the most current revision of each SOP and DOI is available for reference. Laboratory methods are currently being entered into the QMAS system for the same purpose.

[REDACTED] validated in the end of 2006. This program has been fully operational since March 2007 and is used for the scheduling and documenting of calibration and preventative maintenance operations in both the laboratory and manufacturing.

[REDACTED] has been implemented in order to manage the stability program. The software generates pull schedules and is used for storing all information related to the stability program.

Trackwise is to be utilized in the future in order to document and track Deviations, Investigations, Change Controls, Out of Specification Investigations. The roll-out of this program is anticipated to be by the end of 2007.

TM2000 will be utilized for tracking all training operations.

[REDACTED] -Inventory System will be rolled out in the next 6 months, which will control the inventory of raw materials, bulk product and finished products.

Manufacturing Operations are going to be moved over to the Riverview facility. The first products that will be scheduled for production at the Riverview site will be some of the vitamin products, followed by Digoxin as well as other dry blend products. The Quality Control Laboratory is also set to begin testing and analysts started moving over to the Riverview facility during the course of the current inspection. The QC Laboratory is going to be using Empower Software for their Data Acquisition System for running the HPLCs and will move away from using the TotalChrom System.

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The Central Distribution Center is no longer being used for all distribution functions. These functions were transferred to UPS as of March and April 2007.

**FIRM'S TRAINING PROGRAM**

Since the previous inspection Mr. Vincent D'Esposito, QA Manager, Training has joined Actavis Totowa, LLC. Mr. D'Esposito is responsible for managing the training program, which includes GMP, SOP and QJT training. He is also responsible for maintaining all training records. The training program includes initial GMP training to be given during the first week of employment as well as ongoing GMP training.

**MANUFACTURING OPERATIONS**

Actavis Totowa LLC, Little Falls is a large generic pharmaceutical manufacturer. This facility continues to be responsible for raw material receiving, all manufacturing and testing of drug products. Dosage forms manufactured at this facility include prompt release tablets and capsules and extended release tablets. A complete list of products manufactured at the Little Falls facility was provided and is attached as Exhibit 2.

**MANUFACTURING CODES**

Manufacturing codes were explained to be assigned as follows:

The first digit indicates the year of production [REDACTED]. The following four digits are a consecutive number representing the number Batch produced in that year. [REDACTED] would indicate this was the 1st Batch manufactured in that particular year). The following character is a letter indicating if the Batch was divided by different logos or customers. [REDACTED] would indicate the first logo or customer and [REDACTED] would indicate the second). The last digit would be indicative of the packaging configuration. [REDACTED] would represent the first packaging configuration and [REDACTED] would indicate the second).

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**COMPLAINTS**

Complaints were reviewed during this inspection. A discussion was held regarding the length of time taken to close complaints. Complaints received in the last three months have been handled in a timely manner. (Please see Discussion with Management Section of this report for additional details.)

**INSPECTIOINAL COVERAGE**

The Quality, Production, Laboratory Control, Materials and Facilities & Equipment Systems were covered during the current inspection and corrections made since the previous inspection were verified. Pre-approval coverage was also provided to [REDACTED]

Items reviewed during this inspection include, but were not limited to:

Facility Tour  
[REDACTED]

Development Report  
Regulatory Correspondence  
Standard Operating Procedures (SOPs)  
Receiving and Warehousing Procedures  
Equipment Cleaning and Usage Logs  
Equipment Calibration and Preventive Maintenance  
Analytical Raw Data (raw material, finished product, stability)  
Batch Records (masters and executed)  
OOS Investigations  
Production Investigations  
Rejected Batches  
Recall: Dantrolene 25 mg Capsules  
Field Alert: Carisoprodol Aspirin and Codeine Phosphate Tablets  
Materials in Quarantine  
Deviations and Investigations  
Change Controls  
Complaints

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GMP Training  
Equipment Qualifications  
Cleaning Validations  
Recovery Studies  
Process Validations  
Annual Product Reviews  
Method Validations  
Stability Data  
Laboratory Notebooks  
TotalChrom Data Acquisition System  
Pest Control  
Bin Cards  
Micro Control Solutions Stability Systems II  
QSIP  
Corrections to previous FDA 483

[REDACTED]

[REDACTED]

[REDACTED]

The CMC section of the application was reviewed as well as the development report, specifications for raw materials and finished product, raw analytical data for raw materials, in-process samples, finished product, and stability samples, method validations, revisions to methods, reference standards, the executed Batch record, equipment qualifications, calibrations and preventive maintenance, and cleaning logs. A flow diagram of the manufacturing process was provided and is attached as (Exhibit 7).

All in-process and finished product testing was performed at the Taft Road Facility. This data was reviewed at the Taft Road facility as part of this inspection.

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I explained that a [REDACTED] was to be submitted with respect to [REDACTED]

**FIELD ALERT: CARISOPRODOL ASPIRIN AND CODEINE PHOSPHATE TABLETS,  
LOT # 60484A1.**

An OOS result for assay was received on 8/21/07, during the testing of Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1 at the twelve-month stability test point. The result was low for Codeine, [REDACTED] (Exhibit 8). The original flasks were reshaken and the results were similar [REDACTED] confirming the original results (Exhibit 9). Upon investigation it was noticed that the blend used in this analysis was originally prepared on 8/6/07 and therefore it was determined that a new composite powder should be prepped and the analysis should be repeated. The results for this analysis were obtained on 8/21/07 and were [REDACTED]; once again confirming the original results (Exhibit 10). A second analyst performed a repeat test on 8/28/07 with double the original sample prep and the results were [REDACTED] (Exhibit 11). These were all in specification, but were low and therefore could not be used to disqualify the original results. Three additional bottles of this lot were pulled from stability and tested on 9/6/07 (Exhibit 12). These additional samples also gave [REDACTED]. The field alert was filed on 9/7/07 (Exhibit 13), which was in excess of three days of the original OOS results (Please see FDA 483, Observation 1).

The testing of Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484AQ (500 count bottles) was discontinued because of discoloration of the tablets and because the tablets were OOS for Salicylic acid (Exhibit 14). Although the notation in the laboratory notebook indicates "the batch is on the market as well", this is not a marketed packaging configuration. I indicated that if the QC laboratory had been testing the tablets, an OOS investigation should have been opened regarding the OOS for Salicylic acid. I indicated that the only difference between Lot # 60484AQ and Lot # 60484A1 was the packaging configuration and therefore Lot # 60484A1 should have been looked at more closely when OOS results were received for Lot # 60484AQ. In addition, no trend in high salicylic acid results was noted at the nine-month stability test point for Lot # 60484AQ (500 count) or Lot # 60484A1 (100 count) although results were trending higher than normally seen at the nine-month test point (Exhibit 15). Mr. Talbot stated that a retain of Lot # 60484A1 was tested on 9/1/07 and the results seemed higher for Salicylic acid than seen in other lots.

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I indicated that there were long gaps between the original testing on 8/21/07 and the repeat test performed on 8/28/07 and again between 8/28/07 and 9/7/07. Mr. Talbot explained that this was an error made in scheduling when the Laboratory Supervisor was on vacation. He indicated that the testing that actually occurred on 8/28/07 had been scheduled to take place on 8/22/07. The schedule had been changed while the Supervisor was on leave on 8/22, 8/23 and 8/24/07. On 8/27/07 the testing was rescheduled and took place on 8/28/07. I explained that once the original results had been confirmed, the Field Alert should have been issued.

All retains of Carisoprodol Aspirin and Codeine Phosphate Tablets 200 mg / 325 mg / 16 mg have been tested during the course of this inspection with no other failing results. The investigation was not completed at the time of the close of the inspection (Exhibit 16).

There have been no complaints on Lot # 6048AQ.

**RECALL**

A recall was initiated on Dantrolene Sodium Capsules after one of the process validation batches for Dantrolene Sodium Capsules 25 mg Lot # 60244A failed to meet specifications for dissolution at the 12-month stability test point on May 9, 2007. A Field Alert was initiated on May 11, 2007, and all three process validation lots of Dantrolene Sodium Capsules, 25 mg were recalled, namely Lot #'s 60243A, 60244A and 60245A. The recall was initiated on 6/7/07, with the first letter being sent out on 6/11/07 and a second notice sent out on 9/11/07. There has been a 40% response to the Recall Notice to date. The return of recalled product is being handled by Capital Returns, a contract company operating out of Minnesota. The district will continue to receive updates on this recall until completion. The recall is expected to be complete by the end of 2007.

Additional failures have occurred in the testing of Dantrolene Sodium Capsules. On May 2, 2007, Dantrolene Sodium Capsules 50 mg Lot # 70333A failed to meet finished product release specifications and was rejected. This was the first lot produced after completion of process validation. On June 27, 2007, Dantrolene Sodium Capsules 100 mg Lot # 70498A, also failed to meet finished product release specifications and was also rejected. This 100 mg Lot was the first lot produced after completion of process validation for a reformulation was made in order to remove 5% of the original amount of lactose. Both of these failures were also dissolution failures. The firm has ceased production of Dantrolene Sodium Capsules at this time and the product formulation is being evaluated by the Research and Development Group.

Currently, six lots of Dantrolene Sodium Capsules remain on the market: three lots of 50 mg capsules and three lots of 100 mg capsules, all six of which are process validation batches for which stability data shows no problems with dissolution results to date. None of these batches have gone to S2 testing for dissolution while on stability.

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### **MARKET WITHDRAWAL**

There was a market withdrawal on one lot of Meclazine HCl Tablets (Lot # 61000A1) due to a mislabeling of the product as Rx-only when this product is non-Rx. This discrepancy was brought to the attention of Actavis through a complaint on 12/28/06. The template was discovered to have been incorrect for this product only. The error occurred when the templates were changed for all labeling in order to change the name that appeared on the labeling from Amide to Actavis. This is the only lot of Meclazine HCL Tablets distributed with the labeling error. The labeling group is located in Baltimore.

### **BLEND UNIFORMITY**

Planned Deviation PD-07-006 was initiated on 1/17/07 in order to allow for the delivery of blend samples to the QC Laboratory as slugs. There was a high rate of blend uniformity failures due to this planned deviation. PD-07-006 called for all blends of 50 mg active or lesser concentration to be prepared as slugs and delivered to the laboratory for testing. Previously, there had been no issues with failure to meet blend uniformity specifications for any products. Investigations revealed that the failures were due to using thieves without the appropriate volume cavities and manipulating the slugs to create the correct weight of a sample for testing. There were additional manipulations of the samples in the way in which weights were measured through transferring the sample to the scale and then back into weigh paper envelopes, which were then taken to the lab. A Corrective and Preventive Action Request (CAPA) was opened on 3/19/07, which targeted the deficiencies noted above. New thieves and inserts were purchased in order to obtain the correct sample sizes and QA Samplers were trained to use pre-weighed glass vials in order to collect the samples instead of the previously used weigh paper envelopes.

I discussed the fact that some investigations into the OOS results for blend uniformity failed to document the sampling procedures and the planned deviation as a possible cause for the OOS results. These investigations include : Investigation Log No. 07-008 for Quinipril Hydrochloride and Hydrochlorothiazide Tablets 20/12.5 mg Lot # 70111A, Investigation Log No. 07-009 for Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5/1.5 mg Lot # 70097A and Investigation Log No. 07-010 for Hydroxyzine Hydrochloride Tablets 10 mg Lot # 70132A, attached as Exhibits 17, 18 and 19, respectively. All three Lots were rejected.

There are continuing problems with blend uniformity results with Pentazocine Hydrochloride and Acetaminophen Caplets as well as Pentazocine Hydrochloride and Naloxone Hydrochloride Tablets even after moving to the glass vials. Grounding of the thief is being explored in order to reduce any

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static charges from the sampling procedure. In addition, a CBE-30 has been submitted in order to change blend uniformity specifications to be in-line with content uniformity specifications with the use of an Acceptance Value in specifications instead of RSD.

**QUALITY SYSTEM**

The Quality System was evaluated during the current inspection. There have been many changes in personnel and in the quality systems since the previous inspection (Please see "Changes in Personnel and Operations" and "Voluntary Corrections" sections of this report for details).

Annual product reviews, complaints, deviations, investigations, change controls, rejected materials, stability failures, recalls, field alerts, quarantine products, process validations, computer validations, and training items were reviewed as part of the coverage to the Quality System.

Please see Observation #1 regarding Field Alerts.

**FACILITIES AND EQUIPMENT SYSTEM**

Coverage was provided for the Facilities and Equipment System. Equipment/Room Cleaning and Usage Logs, Equipment Calibration and Preventive Maintenance, Change Controls, Equipment Qualifications, Cleaning Validations, Recovery Studies, Detergent Studies, Equipment Identification Practices, and Pest Control Documentation were reviewed under this system.

**MATERIALS SYSTEM**

SOPs, receiving and warehousing procedures, FIFO, material inventory cards, storage conditions, location identification practices, storage under quarantine, sampling, release and rejection, and distribution procedures were reviewed as part of the coverage to the Materials System. A tour of the warehouse was provided and warehousing procedures were observed.

**PRODUCTION SYSTEM**

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Coverage of the Production System included training; change control, deviations, investigations, batch record documentation practices, equipment identification practices, process validation, in-process sampling and testing, hold times, in-process and finished product specifications, adherence to batch manufacturing records, master batch records and equipment cleaning and use logs. A tour of Production was provided and manufacturing operations were observed including dispensing, blending, compression and encapsulation.

Please see FDA Observation #3 regarding the documentation of deviations.

**LABORATORY CONTROL SYSTEM**

The Quality Control Laboratory consists of [REDACTED] individuals, who are broken down into five teams: Finished Product and Stability, Raw Material/In-Process, Technical Services, Instrumentation/Metrology, and Laboratory Compliance. Major instruments include [REDACTED] HPLCs, [REDACTED] spectrophotometers, [REDACTED] dissolution baths, [REDACTED] particle size analyzers, [REDACTED] disintegration tester, [REDACTED] polarimeter, [REDACTED] autotitrators and [REDACTED] fluorometers. The scheduling and documentation of calibration and preventive maintenance for all laboratory instruments is controlled by the CALMAN computer system. A tour of the Laboratory was provided, notebooks were reviewed for sample preparations and completeness, reagents and sample preparations as well as standards were appropriately identified throughout the laboratory. Up to date methods and specifications were available within the laboratory and raw data was reviewed both in notebooks and on the TotalChrom Data Acquisition System.

Please See FDA Observation #2 regarding the stability program.

The laboratory at the Taft Road facility was also visited during this inspection (on 9/26/07) in order to review raw data on the TotalChrom Data Acquisition System pertaining to [REDACTED]

**OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE**

Present for the closeout meeting were:

Scott Talbot, Site Head of Quality

Apurva Patel, Director, Site Operations

Phyllis Lambridis, VP, Quality Compliance for Actavis U.S.

Jasmine Shah, VP, Regulatory and Medical Affairs for Actavis, U.S.

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Wanda Eng, Sr. Director Corporate Compliance for Actavis U.S.  
Garret Wolan, Compliance Manager for Actavis U.S.

**Observations listed on form FDA 483**

**QUALITY SYSTEM**

**OBSERVATION 1**

An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.

Specifically, a Field Alert was not submitted within three working days of receipt of out of specification results during the stability testing of Carisoprodol, Aspirin and Codeine Phosphate Tablets, 200 mg / 325 mg / 16 mg, Lot 60484A1 at the twelve-month stability test interval. The original out of specification result was received on 8/21/07, results were confirmed as OOS on 8/28/07, but the Field Alert was not submitted until 9/7/07.

Reference: 21 CFR 314.81(b)(1)(ii)

**Supporting Evidence and Relevance:**

An OOS result for assay was received on 8/21/07, during the testing of Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1 at the twelve-month stability test point. The result was low for Codeine, [REDACTED] (Exhibit 7). The original flasks were reshaken and the [REDACTED] confirming the original results (Exhibit 8). Upon investigation, it was noticed that the blend used in this analysis was originally prepared on 8/6/07 and therefore it was determined that a new composite powder should be prepped and the analysis should be repeated. The results for this analysis were obtained on 8/21/07 and were [REDACTED], once again confirming the original results (Exhibit 9). A second analyst performed a repeat test on 8/28/07 with double the original sample prep and the results were [REDACTED] (Exhibit 10). These were all in specification, but were low and therefore could not be used to disqualify the original results. Three additional bottles of this lot were pulled from stability and tested on 9/6/07 (Exhibit 11). These additional samples also gave [REDACTED]. The field alert was filed on 9/7/07 (Exhibit 12), which was in excess of three days of the original OOS results.

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I indicated that there were long gaps between the original testing on 8/21/07 and the repeat test performed on 8/28/07 and again between 8/28/07 and 9/7/07. Mr. Talbot explained that this was an error made in scheduling when the Laboratory Supervisor was on vacation: He indicated that the testing that actually occurred on 8/28/07 had been scheduled to take place on 8/22/07. The schedule had been changed while the Supervisor was on leave on 8/22, 8/23 and 8/24/07. On 8/27/07 the testing was rescheduled and took place on 8/28/07. I explained that once the original results had been confirmed, the Field Alert should have been issued.

The testing of Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484AQ (500 count bottles) was discontinued because of discoloration of the tablets and because the tablets were OOS for Salicylic acid (Exhibit 13). Although the notation in the laboratory notebook indicates "the batch is on the market as well", this is not a marketed packaging configuration. I indicated that if the QC laboratory had been testing the tablets, an OOS investigation should have been opened regarding the OOS for Salicylic acid. I indicated that the only difference between Lot # 60484AQ and Lot # 60484A1 was the packaging configuration and therefore Lot # 60484A1 should have been looked at more closely when OOS results were received for Lot # 60484AQ. In addition, no trend in high salicylic acid results was noted at the nine-month stability test point for Lot # 60484AQ (500 count) or Lot # 60484A1 (100 count) although results were trending higher than normally seen at the nine-month test point (Exhibit 14). Mr. Talbot stated that a retain of Lot # 60484A1 was tested on 9/11/07 and the results seemed higher for Salicylic acid than seen in other lots.

All retains of Carisoprodol Aspirin and Codeine Phosphate Tablets 200 mg / 325 mg / 16 mg have been tested during the course of this inspection with no other failing results. The investigation was not completed at the time of the close of the inspection (Exhibit 15).

There have been no complaints on Lot # 6048AQ.

All present at the closeout agreed with this Observation.

**LABORATORY CONTROL SYSTEM****OBSERVATION 2**

The written stability testing program is not followed.

Specifically, the following products were not tested at the 36-month stability test point:  
Meperidine Hydrochloride and Promethazine Hydrochloride Tablets, 50 mg / 25 mg, Lot 4117A1

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Dexchlorpheniramine Maleate ER Tablets, 6 mg, Lot 4092A1

Methenamine Mandelate Tablets, 1.0 mg, Lot 4120A

Chlordiazepoxide Hydrochloride and Cliniidium Bromide Capsules, Lot 3480A3

The above listed products were tested at a later date, but the cause for not conducting the testing at the appropriate time was due to incorrect assumptions that the product need not be tested due to changes in expiration dating.

Reference: 21 CFR 211.166(a)

**Supporting Evidence and Relevance:**

According to Investigation 07-031 (Exhibit 20), Meperidine Hydrochloride and Promethazine Hydrochloride Tablets, 50 mg / 25 mg, Lot 4117A1, Dexchlorpheniramine Maleate ER Tablets, 6 mg, Lot 4092A1 and Methenamine Mandelate Tablets, 1.0 mg, Lot 4120A were not tested at the 36-month stability test point. According to Investigation 07-037 (Exhibit 21) Chlordiazepoxide Hydrochloride and Clinidium Bromide Capsules, Lot 3480A3 was also not tested at the 36-month stability test point.

The above listed products were tested at a later date, but the cause for not conducting the testing at the appropriate time was due to incorrect assumptions that the product need not be tested due to changes in expiration dating. The stability coordinator mistakenly these products did not need to be tested because the product lines had changed expiration dating from 36 months to 24 months. However, these particular lots of product were manufactured under a 36 month expiry and therefore required testing. I indicated that one should not assume testing is unnecessary when products are due for testing.

All present at the closeout agreed with this Observation.

**PRODUCTION SYSTEM**

**OBSERVATION 3**

Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically, the Standard Operating Procedures "Investigation of Deviations" (SOP # 0033) and "Investigation of Out of Specification Results" (DOI # QC-059) are not followed in that Investigations are not initiated when a deviation or out of specification result is detected and are not closed within 30 days. In addition, interim reports are not always written to document justification for investigations to remain open after each 30 day interval.

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For example:

- a) No investigation for Buspirone HCl Master Blend Lot 70683A was initiated as of 9/25/07 although the blend was placed on hold for unidentified particles discovered in the blend on 9/6/07.
- b) An investigation for low yield of Carisoprodol, Aspirin and Codeine Phosphate Tablets USP 200/325/16mg, Lot 70488A was not initiated when the yield was determined to by [REDACTED] on 7/9/07. The batch record was signed off as reviewed and approved by production management prior to the initiation of the investigation on 7/18/07.
- b) Investigation of Deviation Reports 07-003 and 07-004 were issued on 1/19/07 and 1/29/07, respectively, but were not closed until 5/25/07.
- c) Only one interim report was written for investigation 07-013, which was open from 3/14/07 through 7/21/07.

Reference: 21 CFR 211.100(b)

**Supporting Evidence and Relevance:**

Standard Operating Procedures "Investigation of Deviations" (SOP # 0033) (**Exhibit 22**) and "Investigation of Out of Specification Results" (DOI # QC-059) (**Exhibit 23**) are not followed in that Investigations are not initiated when a deviation or out of specification result is detected and are not closed within 30 days. In addition, interim reports are not always written to document justification for investigations to remain open after each 30 day interval.

A Hold Notification Form dated 9/6/07 indicated that Buspirone HCl Master Blend Lot 70683A was placed on hold for unidentified particles discovered in the blend on 9/6/07 (**Exhibit 24**). No investigation was initiated for this blend as of 9/25/07. In addition, there was no notation in the batch record until I asked to see the batch record. The date of 9/25/07 was applied to the record on the date that I asked to see the batch record as an investigation had not yet been initiated (**Exhibit 25**).

An investigation for low yield of Carisoprodol, Aspirin and Codeine Phosphate Tablets USP 200/325/16mg, Lot 70488A was not initiated when the yield was determined to by [REDACTED] on 7/9/07. The batch record was signed off as reviewed and approved by production management prior to the initiation of the investigation on 7/18/07 (**Exhibit 26**).

Investigation of Deviation Reports 07-003 and 07-004 were issued on 1/19/07 and 1/29/07, respectively, but were not closed until 5/25/07 (**Exhibits 27 and 28**). I discussed the importance of concluding investigations and closing them out within reasonable timeframes.

Only one interim report was written for investigation 07-013, which was open from 3/14/07 through 7/21/07 (**Exhibit 29**). There should be justification provided in interim reports, to be written each 30 day period, in order to identify why an investigation remains open and what information may still be pending and why.

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All present at the closeout meeting agreed with this Observation.

**REFUSALS**

There were no refusals throughout the course of this inspection.

**GENERAL DISCUSSION WITH MANAGEMENT**

The following items were discussed both during the inspection and again at the closeout meeting:

-Cleaning within 30-day time frame

During the tour of manufacturing, I identified one case in which Tablet Press #60 had not been cleaned before use after the 30-day time frame designated in SOP #0012 had been passed.

Maltraxone HCl Tablets 50 mg batch 706304 had been compressed on this tablet press on 8/2/07. The equipment had been cleaned on this date, but had not been cleaned again before the use of the equipment in the compression of Betaxolol HCL Batch 70605A on 9/5/07 although this time period between cleaning and the following use was in excess of 30 days. I did not observe any other instances in which equipment had not been cleaned when required.

-Passwords

During the second day of the inspection, a password was required to view the CMC section on the computer provided in the conference room. The individual logged on to the computer was not available and a second individual attempted to enter a password given to him over the phone in order to open the CMC section for my viewing. A discussion was held regarding the importance of password protection. I explained that although the only data available on the computer could not be manipulated in any way, it is not a good practice to share passwords of any kind.

-Obsolete version of specifications available

When I asked for the current specifications for Dihydrocodeine Bitartrate raw material, I was provided with revision 00, although the current Revision is actually 01. The Revision 00 of the specifications came from the QC Laboratory. I explained that no Revisions except the current Revision should be available unless it is clearly identified as obsolete. This situation will be remedied with the QMAS system.

-Daily checks for balances

The daily check made for balance #985 was observed to not bracket the usage range of the scale. It was noted that the external calibration does cover the entire usage range. I suggested at least covering the low and high points of the usage range during daily checks.

-Inventory of bulk controlled on container labels

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In reviewing the bulk inventory of Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Capsules, RBR-2611, it was noted that the inventory is not controlled on the Batch Record Log as it is for packaged product. The deductions on the container labels did not include all deductions and the SOP "Batch Record Logs" (SOP #020) did not include instructions on how or where to document the inventory control of bulk product.

**-Timeliness of investigations****-Drixoral Tablets, Lot # 60379A**

During the coating of Drixoral Tablets-Barrier Coated Tablets, Lot # 60379A, the third coating pan of tablets was not of sufficient size to be coated appropriately according to the batch record. The MPR guideline for each pan load for barrier coating based on theoretical weight is [REDACTED]. The third pan load was [REDACTED] below the lower limit). There was no planned deviation in order to allow this pan to continue the coating process. -The product was rejected. I indicated that the yield specifications should be evaluated because this batch met yield specifications throughout production and there were still not enough tablets available to complete coating according to the MPR guideline.

**-Pentazocine Hydrochloride Acetaminophen Tablets (broken tablets)**

Investigation 06-036 into the repeated complaints of broken Pentazocine Hydrochloride Acetaminophen tablets did not capture the fact that three of the six complaints referred to the same lot of Pentazocine Hydrochloride Acetaminophen, namely Lot # 5485A1. The investigation also indicated that no testing of retains was warranted, and there was no reference to investigating the type of container closure used in the packaging of each lot. Two packaging configurations may be used based on the customer; one is a [REDACTED] round bottle and the other is a [REDACTED] rectangular bottle. The possible need for additional cotton within the bottles was not explored and shipping conditions were not discussed. I explained that this investigation could have been more thorough.

**-Procedure for Handling of Complaints**

SOP: 34 Revision 6 does not include how to handle a complaint that comes from a customer for whom product is contract manufactured. I indicated that this should be included in the scope or the procedure should indicate if a separate system is being used to track complaints received from such customers.

-OOS # 07-007 Hydromorphone Hydrochloride Tablets was not initiated within 24 hours. This OOS investigation was initiated nine days later. In addition this investigation was open from 1/19/07 through 5/24/07. More recent investigations have been initiated immediately and most have been closed within the designated timeframe.

**-Cilostazol Tablets Process Validation Batch High Yield**

The first of three process validation batches for Cilostazol Tablets, 100 mg had a high yield of [REDACTED] after granulation. In investigation # 07-020, this high yield was attributed to moisture from production. The investigation did not determine any corrective action was necessary although the other two process validation batches exhibited yields of over 100% after granulation as well. I indicated that a corrective action does not have to be an immediate action, but can also consist of measures such as trending the next 5-10 batches produced in order to determine what an appropriate moisture specification or yield specification should be.

**-Complaints**

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A discussion was held regarding the timely handling of complaints. While some complaints were observed to take months to resolve with limited information as to why the complaints had not yet been closed, complaints received in recent months have been closed within 30 days.

**-Temperature Mapping of Drying Ovens**

In reviewing the heat distribution studies for the driers (which are expected to operate at 120 degrees F), it was noted that the acceptance criteria of [REDACTED] from the setpoint was designated as an acceptable tolerance for the read-out temperatures of the individual probes. I indicated that this meant that the chamber could range in temperature from [REDACTED]. I explained that the tolerance should be tightened and noted that the actual results have been within approximately [REDACTED] of the setpoint. Mr. Talbot stated that the tolerance will be changed to [REDACTED] for all of the drying ovens.

**-Training**

In reviewing training records, it was noted that several employees did not receive initial GMP training until months after they were hired. For example one QA Inspector, hired on 3/19/07, did not receive GMP training until 7/13/07, whereas initial GMP training is to be given within the first week of employment. Mr. Vincent D'Esposito, QA Manager, Training has recently joined Actavis Totowa and is responsible for managing the training program, which includes GMP, SOP and OJT training. Recently hired individuals have received initial GMP training and the training program has been updated since Mr. D'Esposito began managing the training program.

**-TLC methods for Impurity Testing**

It was noted that the testing for impurities in Clordiazepoxide HCl and Clidinium Bromide Capsules is conducted by HPLC. I indicated that this method would not reveal any unknown impurities and that it is not a stability indicating method. Production of this product has been discontinued.

**-Methods to be Validated prior to use on Submission Batch**

As indicated in a previous inspection, all methods should be validated prior to use on an ANDA submission batch. The methods for the testing of Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Capsules 356.4 mg / 30 mg / 16 mg, were not validated until after the testing of submission batch RBR-2611. This batch was manufactured in 2006, prior to the change in the procedure indicating that submission batches will not be tested unless the method has been validated. The methods used in testing this batch are the same as those that are currently validated.

**SAMPLES COLLECTED**

Profile Sample # 377413 was collected at the close of this inspection.

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**VOLUNTARY CORRECTIONS**

Corrections to the previous FDA 483 were reviewed with Ms. Wanda Eng, Sr. Director Corporate Compliance for Actavis U.S. The previous 483 Observations and the associated corrections appear below.

**OBSERVATION 1**

The quality control unit lacks authority to fully investigate errors that have occurred.

Specifically, there is no assurance that the Quality Unit can be relied upon to fulfill its responsibilities to assure that all drug products released to the marketplace meet the requirements for identity, strength, quality, and purity that they purport to have. Batches of drug products that initially failed to meet release specifications were released into interstate commerce without being fully investigated, all laboratory data was not included with the batch records and manufacturing deviations were not always documented.

Corrections:

A number of individuals have been hired and/or have been promoted since the previous inspection, including, but not limited to:

Phylis Lambridis, Vice President of Quality and Compliance, U.S.

Scott Talbot, Site Head of Quality

Paul Galea, Director of Quality Systems

Vince D'Esposito, Training Manager

Swapan Roychowdhury, Director, Quality Control

Jisheng Zhu, Quality Control Manager

Elina Novikov, Stability Manager

Chrystal Day, Stability Coordinator

Joaquin Mejia, Stability Coordinator

Bernard Glover, CAPA and Complaints Specialist

Mike Ponzo, Investigation Specialist

Tony Castaluzzo, Director, Quality Assurance, Totowa (located in Riverview facility)

Elizabeth Guarch, Validation Manager

Irina Kotkova, Validation Specialist

Lauren Miranda, Quality specialist

Pam Barckett, Documentation Specialist

In addition, four new analysts and two temps have been brought into the QC Laboratory. An additional two analysts were hired during the course of the inspection.

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Since the previous inspection, the number of individuals in the Quality Assurance Department has increased from [REDACTED]. This is equivalent to a change in the ratio of Operation/Quality personnel from [REDACTED]

All Standard Operating Procedures (SOPs) and Departmental Operating Instructions (DOIs) have been reviewed and uploaded into QMAS, a validated computer system, which will enable employees to access all procedures and instructions on-line and will ensure that only the most current revision of each SOP and DOI is available for reference. Laboratory methods are currently being entered into the QMAS system for the same purpose.

[REDACTED] in the end of 2006. This program has been fully operational since March 2007 and is used for the scheduling and documenting of calibration and preventative maintenance operations in both the laboratory and manufacturing.

Microcontrol Solutions Stability System II has been implemented in order to manage the stability program. The software generates pull schedules and is used for storing all information related to the stability program.

Trackwise is to be utilized in the future in order to document and track Deviations, Investigations, Change Controls, Out of Specification Investigations. The roll-out of this program is anticipated to be by the end of 2007.

Consultants were hired and retained over the last year to perform a number of functions. They were utilized in the re-training of Laboratory and Quality Assurance personnel in the areas of Deviations, GMPs and Good Documentation Practices, as well as additional refresher trainings. All process validations were evaluated for accuracy and completeness and all equipment qualifications for production and laboratory equipment/instruments were reviewed. For all products on the market since the previous inspection through Feb 2007 that were associated with any type of deviation or investigation, consultants reviewed all associated Deviations, QA Investigations, OOS Investigations, and Batch records. In addition, a representative sample of batches manufactured was also selected for full review. The review of this representative sample should be completed in the near future.

The Quality Systems Improvement Plan (QSIP) was initiated as of August 29, 2006. QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAPA, Documentation, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance/Audits, Warehouse/Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. A copy of the plan was provided and is attached as Exhibit 6. Actavis has been updating Compliance Branch regularly regarding the status of their progress in QSIP. Progress was reviewed during the current inspection and many positive changes have been made since the previous inspection due to the implementation of this program.

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For additional corrective actions please see each following Observation.

**OBSERVATION 2**

Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.

Specifically, the Quality Unit failed to assure that laboratory notebooks include all data generated during testing and that analysts document in their laboratory notebook all sample preparation and testing at the time it occurs. Additionally, SOP QC-59 Investigation of out of specification test Results (OOS) is not always followed. For example:

- a) On 1/11/06, during content uniformity testing of Ursodiol Capsules, Batch 51083A, the analyst noticed that the first two capsules were out of specification and he aborted the run. The audit trail for the laboratory data acquisition system does not indicate that the run was aborted and the analyst did not print the sample results or report the failing results in the laboratory notebook. An investigation was initiated and it concluded that a sample dilution error was made. A review of the lab notebook shows the sample dilution value in the laboratory notebook was over written, without being signed and dated as required. Additionally, a review of the laboratory notebook page showing the sample preparation and a photocopy of the same page in the investigation report, revealed that they were not the same. Changes were made in the laboratory notebook after it was signed and approved.
- b) [REDACTED] for Sample 1-1 for pooled dissolution of Oxycodone and Acetaminophen Capsules Batch # 5259A was not documented in Laboratory Notebook # 700-34 and was not attached to the hard copy chromatograms. An additional injection was made for Sample 1-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.
- c) [REDACTED] for Capsule-2 dissolution sample for Amidrine Capsules, Batch # 5637A, was not documented in Laboratory Notebook # 349-08. An additional injection was made for Capsule-2 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.
- d) Quinapril Batch # 60423A was tested on 5/31/06 and failed to meet the specification for impurities. A new sample preparation was prepared and the batch was retested within the same chromatographic run, without prior approval as required. The original results and the results of the new sample preparation appear together in the laboratory notebook not one after the other. The out of specification (OOS) results for high impurities were invalidated without any scientific justification and the batch was retested and released. This same batch had a low yield due which was attributed to compression problems. The entire batch was compressed below the action limit for hardness, which resulted in the rejection of approximately 50,220 broken tablets, or 4.25 % of the batch.
- e) The original result of 89.9% for Assay-1 in the analysis of Buspirone HCl 5 mg Tablets Batch # 3144A, 24 month stability was not documented in Laboratory Notebook # 666-01. An additional injection was made for Assay-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated.
- f) There was no notation in Laboratory Notebook # 349-07 although the original result for Assay-1 of Amidrine Capsules Batch # 5113A did not show any peaks (due to injection of the wrong vial). An additional injection was made and results were recorded without documenting the discrepancy. A note was later squeezed into the Laboratory Notebook just above the "Conclusion" section of the analysis.
- g) On 10/7/05 during the testing of Hyoscyamine Sulfate Tablets, Batch 5823A, one assay value was approximately double the expected value. The failing results were attributed to a transcription error in the

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sample weight. The failing results were not recorded in the laboratory notebook and were not printed from the laboratory data acquisition system.

**Corrections:**

All analysts have been retrained since the previous inspection and have had specific training on documentation practices as well as additional training on how to conduct adequate deviation investigations. Any changes to a chromatographic sequence now require supervisory approval. New procedures have been put into place in order to ensure that all data is documented within laboratory notebooks. These procedures include: QC 002: Laboratory Notebook and Review Procedures and QC 106: Evaluation of Laboratory Error. In addition DOI QC 059 was revised to state "If the error is observed after sample measurement began, the analysis should be carried out to the end without interruption".

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**OBSERVATION 3**

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, there is no assurance that the Quality Unit can detect discrepancies in reports for which they are responsible. Data and reports reviewed and approved by the Quality Unit were not accurate and complete and did not adhere to established procedures. In addition, changes are not always documented in the change control system. For example:

- a) A page was left blank in Notebook # 605-06 between the original and repeat testing of Carisoprodal, Aspirin and Codeine Tablets, Batches 2020A, A1, 36-month stability samples and 3027A1, 12-month stability samples, for Codeine Phosphate Assay. The page was later written on by the Director of QC indicating why the previous results had been disqualified.
- b) The Process Validation Report for Ursodiol Capsules USP 300 mg (2,000,000 capsules), dated 6/23/06, did not mention the OOS result received during the Content Uniformity testing of Batch 51083A.
- c) The Process Validation Report for Hydroxyzine HCl USP 50 mg (500,000 tablets), dated 8/9/05, did not mention the OOS result received during the Blend Assay testing of Batch # 5519A.
- d) The current inventory of the exhibit batch listed in ANDA 40706/000: Benztropine Mesylate 2 mg Tablets states "RBR-1661: 7667 tablets stored for bulk stability evaluation." The exhibit batch for Benztropine Mesylate 2 mg Tablets is RBR 2137. RBR-1661 is the exhibit batch for Hydroxyzine HCl. Additionally, the results for bulk stability of Benztropine Mesylate reflect that of the testing of finished packaged product and not that of the bulk (see Observation # 7).
- e) The compression page of the batch record for Quinipril was changed to add a statement about timeframes and how to pack the blend. This change did not go through the change control system.

**Corrections:**

Standard operating procedures are now being followed. All data is reviewed by laboratory managers. The following SOP's have been revised: SOP 0065: Change Control, SOP 0079: CAPA Program, DOI QC 106: Evaluation of Laboratory Error and QC 002: Laboratory Notebook and Review Procedures. All CAPAs will be trended and reviewed by QS on a monthly basis as per SOP

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0079. Step 5.3.2.2 of Procedure SOP 0055: Process Validations, effective 9/6/07 states to justify and discuss deviations in validation reports. A current process validation report was reviewed which did discuss a failure to meet yield specifications. In addition, QC 059: Investigation of OOS and Suspect test results has also been updated.

A QA coordinator has been hired to manage change controls. SOP 0065: Change Control has been updated.

A letter was sent to CDER to correct the exhibit batch number for Benztropine Mesylate that was filed in the ANDA.

**LABORATORY CONTROL SYSTEM****OBSERVATION 4**

Written records are not always made of investigations into the failure of a batch or any of its components to meet specifications.

Specifically, investigations were not conducted when out of specification (OOS) results were generated. Samples were retested and the original results were not invalidated. For example:

- a) No initial investigation was made into the out of specification Assay-1 result for Buspirone HCl 5mg Tablets Batch # 3144A, 24-month stability [REDACTED] when the result was obtained on 3/20/05. Assay-1 was repeated within the same chromatographic run. There was no documented investigation until 7/15/05 and retesting did not include a re-injection of the same sample vial.
- b) No initial investigation was made into the out of specification result for the Left-Slope Blend Assay sample of Hydroxyzine HCl Tablets, 50 mg Batch # 5519A [REDACTED] when the result was obtained on 6/24/05. The analysis of the Left-Slope sample was repeated within the same chromatographic run. There was no documented investigation until 7/27/05 and retesting did not include a re-injection of the same sample vial.
- c) No initial investigation was made for an out of specification assay result for Quinapril HCl and Hydrochlorothiazide Tablets, 10/12.5 mg, Batch # 4180A1, 12-month stability [REDACTED] when the result was obtained on 5/24/05. The analysis was repeated with new sample solutions within the same chromatographic run. There was no documented investigation until 7/22/05, which indicated that the sample solutions were prepared using the average tablet weight instead of twice the average tablet weight, which resulted in peak areas of approximately 50% of the standard response. This explanation should not have resulted in an OOS result. The investigation did not address the OOS result generated.
- d) No initial investigation was made for an out of specification blend uniformity result for Oxycodone HCl Tablets, 15 mg, Batch # 5023A [REDACTED] when the result was obtained on 1/14/05. The analysis was repeated within the same chromatographic run. There was no documented investigation until 7/13/05.
- e) No initial investigation was made for the out of specification result of 65.5% for Sample 1-1 for pooled dissolution of Oxycodone and Acetaminophen Capsules Batch # 5259A, when the result was obtained on 4/14/05. An additional injection was made for Sample 1-1 within the same chromatographic run and was used in the calculations. The original result had not been invalidated and there was no documented investigation

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until 7/19/05.

**Corrections:**

All data generated will be documented in laboratory notebooks and the firm has updated the OOS procedure QC-059: Investigation of Out-Of-Specification and Suspect Test Results, was updated to require all analysts to run all chromatographic testing to completion unless an error is detected before a sample is run. SOP 0033: Investigation of Deviations was updated. All analysts have been retrained.

3<sup>rd</sup> party consultants have reviewed all deviation investigations for both laboratory and manufacturing.

Audit trails are reviewed and all raw data is printed.

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**OBSERVATION 5**

Input to and output from the computer are not checked for accuracy.

Specifically, audits were not conducted of the TotalChrom Data Acquisition System used to run the HPLC instruments during analysis of drug products. Sample injections, processing methods, and sample weights were not reviewed or verified for the accuracy of reported sample results during testing of in-process, finished product and stability samples.

**Corrections:**

New procedures are in place in order to conduct audits of the TotalChrom Data Acquisition System, which is used to run the HPLC instruments. The Graphic Edit Mode function has been disabled in order to ensure accuracy of the laboratory data. DOI QC 155a: Using TotalChrom Client Server Software for Analysis was written to ensure that weights of standards and purity of actives are checked. DOI QC 155p: Procedures to Assign a File Name for TotalChrom Client/Server Data Acquisition was put in place in order to designate a system of assigning file names. DOI QC 155q was written as a procedure to review the accuracy of the data generated by TotalChrom and the audit trail in the Method Sequence file.

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**OBSERVATION 6**

The suitability of all testing methods is not verified under actual conditions of use.

Specifically, there is no assurance that equipment is adequately cleaned due to the deficiencies in cleaning validation studies. For example:

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- a) Cleaning validation was performed for the process trains of the following products without evaluating for sample recovery: Amidal Nasal Decongestant Tablets, Amigesic Caplets 750 mg, Carisoprodol and Aspirin Tablets USP 200 mg/325 mg, Carisoprodol Tablets USP 350 mg, Chlorzoxazone Tablets USP 250 mg and 500 mg, Digoxin Tablets USP 0.25 mg, Guanfacine Tablets USP 2 mg, Meperidine Hydrochloride Tablets USP 100 mg and 50 mg CII, Pemoline Tablets 75 mg CIV, Phentermine Hydrochloride Capsules USP 30 mg and 37.5 mg CIV; Ursodiol Capsules USP 300 mg. (This list is not all inclusive.)
- b) Recovery studies were performed by applying a known amount of active pharmaceutical ingredient directly to a swab instead of applying the active to a coupon or template to replicate the equipment surface from which the active should have been swabbed. Cleaning validation was performed in this manner for the process trains of the following products: Buspirone Hydrochloride Tablets USP 5mg, 10 mg and 15 mg, Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/1.5mg, Mirtazapine Tablets 45 mg, Oxycodone and Acetaminophen Capsules USP 5 mg/500 mg, Oxycodone Hydrochloride Tablets USP 15 mg and 30 mg, Pemoline Tablets 18.75 mg CIV, Pentazocine Hydrochloride and Acetaminophen Tablets 25 mg (base) and 650 mg CIV, Quinaretic (Quinapril HCl and Hydrochlorothiazide Tablets) 20 mg/ 25 mg. (This list is not all inclusive.)
- c) Cleaning Validation studies do not indicate whether or not a cleaning agent was used when cleaning the equipment process train. Equipment cleaning SOPs prior to March 2006 indicated that equipment could be cleaned "using hot water or with approved cleaning agent and water if necessary". In addition, there are no studies to show the cleaning agent is effectively removed from equipment during the cleaning process.
- d) The method for cleaning verification of Benztropine Mesylate was used on 4/28/05 to analyze for residual active after the production of Benztropine Mesylate Tablets RBR-2136 (1 mg) and RBR-2137 (2 mg) although the method was not evaluated for specificity until 5/9/05.

**Corrections:**

Recovery studies were performed on 33 products in a manner in which APIs were spiked onto a coupon, swabbed and then analyzed for recovery. A cleaning validation and recovery study were reviewed during the current inspection in order to verify this corrective action. The SOP for Cleaning Validation has been revised and all cleaning validations are to be included in a matrix approach, the protocol for which has been approved as of 6/27/07. The matrix includes hardest to clean and most potent drug products. Detergent studies were completed on the cleaning agent used. The following procedures have been updated: DOI PRD 002: Room Usage and Cleaning Log, SOP 0012: Production Department Cleaning Procedures, DOI PRD 095: Cleaning Agents used in the Production Areas and DOI PRD 001: Equipment Usage and Cleaning Log.

**OBSERVATION 7**

The written stability testing program is not followed.

Specifically, the stability data recorded as that of bulk stability hold time studies are actually obtained from the testing of the following packaged finished products:

Benztropine Mesylate Tablets, USP 0.5 mg, 1 mg, 2 mg  
Buspirone Hydrochloride Tablets, USP 30 mg

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Imipramine Hydrochloride Tablets, USP 10 mg, 25 mg, 50 mg  
Methimazole Tablets, USP 5 mg, 10 mg  
Phendimetrazine Tartrate Tablets, USP 35 mg

**Corrections:**

At the conclusion of the previous inspection, Mr. Shah explained that the "Stage" Field had been updated such that the Data Processor may now enter "Bulk Tablets" instead of "Finished Product" so that there is no confusion when the Quality Assurance Packaging Supervisor is pulling samples to submit to the laboratory. All of the bulk hold time studies have been repeated on each of the above listed products at time points beyond three months as an immediate corrective action.

Corrections to the stability program have been verified during the current inspection. SOPs and DOIs were updated in order to prevent this situation from reoccurring. The following procedures were revised: SOP0025: Stability Program, DOI: QC 166: Modification to Stability System Software, DOI: QC 167: Logging in and Managing Data using Stability Software System, DOI: QC-041: Stability Chamber Monitoring.

During the inspection, I spoke with Elina Novikov, QC Laboratory Compliance Manager about the new Microcontrol Solutions Stability System II, which has been implemented in order to manage the stability program. She explained that the software generates pull schedules and is used for storing all information related to the stability program. She indicated the program can track schedules, identify trends, store data, indicate when the next test station is due, record date of pull, who pulled the sample, when testing is initiated and when completed. She indicated that older stability data for lots still on the market is currently being added to the computer system. She estimated that all data should be entered by the end of June or July 2008. Ms. Novikov explained that pull dates will no longer be missed according to this corrective action.

**PRODUCTION SYSTEM**

**OBSERVATION 8**

Examination and testing of samples is not done to assure that in-process materials conform to specifications.

Specifically, on numerous occasions quality assurance personnel failed to detect tablets and capsules which did not meet in-process specifications for tablet weight and thickness. SOP-016, "Routine Tablet Press Overcheck", requires a new set of samples be taken when out of specifications results are encountered, this did not occur. For example:

- a) On 7/15/05, during the compression of Carisoprodal Tablets, Batch 5564A, one tablet was documented as

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having an out of specification value of 5.9 kp for hardness on the "QA In-Process Compression Overcheck Data Sheet". The hardness specification is 6.0 - 16.0 kp. The OOS tablet was discovered on 5/19/06, during the compilation of data for the Annual Product Review. Additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

- b) On 11/21/05, during the compression of Carisoprodol , Aspirin & Codeine Tablets, Batch 5904A, one tablet was documented as having an out of specification value of 8.9 kp for hardness on the "QA In-Process Compression Overcheck Data Sheet", the hardness specification is 10.0 - 18.0 kp. The out of specification tablet was discovered on 4/26/06, during the compilation of data for the Annual Product Review. Additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.
- c) On 8/13/05, during the compression of Quinaretic (Quinapril HCL and HCTZ) Tablets, Batch 5659A , one tablet was documented as having an out of specification hardness value of 7.2 kp on the "QA In-Process Compression Overcheck Data Sheet" the hardness specification is 3.0 - 7.0 kp. The out of specification tablet was discovered on 5/19/06, during the compilation of data for the Annual Product Review. Additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.
- d) On 5/19/05, during the compression of Meclizine Hydrochloride Chewable Tablets, Batch 5352A, one tablet was documented as being out of specification for weight and no action was taken. The tablet weight was documented as .237 gm on the "QA In-Process Compression Overcheck Data Sheet" the weight specification is .209 gm to 0.231 gm. The out of specification tablet was not investigated until 12/08/05, when it was discovered during the compilation of data for the Annual Product Review. Therefore, additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.
- e) On 8/16/05, during the compression of Phenazopyridine Hydrochloride Tablets, Batch 5678A, one tablet was documented as being out of specification for weight. The tablet weight was documented as .344 gm on the "QA In-Process Compression Overcheck Data Sheet" and the weight specification is .346 gm to 0.402 gm. The out of specification tablet was not investigated until 6/16/06, when it was discovered during the compilation of data for the Annual Product Review. Therefore, additional tablets were not tested as required by SOP QA-16 and no tablets were rejected which may have been required.

*Please note: There was a typographical error in issuing 483 where Observation 8d and 8e were combined.*

**Corrections:**

A retraining was held for QA personnel (those who perform in-process checks) prior to the close of the previous inspection. An additional inspector was added to the QA manufacturing Inspector Group. DOI QA 016: Routine Tablet Press Overcheck was revised in order to notify supervisor if thickness or hardness do not meet specifications.

**OBSERVATION 9**

Deviations from written production and process control procedures are not recorded and justified.

Specifically, there is no assurance that all manufacturing deviations are documented. For example:

- a) On 11/8/05, Mirtazapine OD Tablets were observed to contain black specks during tablet inspection. Investigation 05-013, into the black specks states that during compression the operators observed the product sticking to the punch tips. The operator was instructed by the supervisor to remove and clean the upper and

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lower punches and then polish the punch tips. The dies and feed frame were also removed and cleaned. None of this was documented on the "Compression Data Sheet" which shows no problems were encountered in compression.

- b) On 5/19/06, during the compression of Quinapril HCL Hydrochlorothiazide Tablets, Batch 60423A, tablets were compressed below the action limit of [REDACTED]. The "Compression Data Sheet" does not indicate that there were any problems with compression although the entire Batch was compressed at a range of [REDACTED] which is below the target tablet hardness of [REDACTED] and below the action limit of [REDACTED]. An investigation for this Batch was not initiated until 6/2/06 when the Batch did not meet yield specifications. The low yield was attributed to broken tablets.
- c) Deviation 05-11 was generated when Pentazocine HCL & Naloxone HCL Tablets, Batch RBR2104 could not be compressed at the required tablet hardness specification of 6-13 kp, on 4/27/05. Compression was stopped and a supplement was filed with FDA to change the hardness specification to [REDACTED]. There is no "QA In-Process Compression Start Up Data Sheet" dated 4/27/06. The only compression start up sheet is dated 5/4/06, which is updated with the new tablet hardness specification of [REDACTED].

**Corrections:**

All operators were retrained. DOI PRD-122: Batch Record Data Entry was updated to require that non-routine occurrences or out of specification results be properly documented. DOI PRD 084: Tablet Press Operation, DOI PRD 169: [REDACTED] Machine, Operation and DOI PRD 232: [REDACTED] Machine Operation was also updated to include "If the tablets/capsules are out of specification, stop the tablet press/encapsulation machine and immediately notify Production and Quality Assurance."

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**OBSERVATION 10**

The master production and control records are deficient in that they do not include complete sampling and procedures.

There is no assurance that all in-process blend samples collected from the mixer are 1 x 3 times the tablet/capsule weight as required. The sample collection is not documented and the sample weight is not measured. For example:

The QA submission form, which is submitted to the laboratory with the in-process blend uniformity samples, does not include the sample weights and the collection of the samples is not recorded in the Batch record.

**Corrections:**

Sample submission forms were revised to include individual sample weights for each of the blend sample locations. These documents have been implemented. Documentation of sample weights is now performed with a target of 2 X dose, and 1 to 3 X is acceptable. The following procedures have been updated: QA 012: Sampling Instructions for Double Cone Blenders, SOP 0031: In-Process and Finished Dosage Testing and DOI QA 043: Sampling Instructions for Twin Shell Blenders.

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FACILITIES & EQUIPMENT SYSTEM

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OBSERVATION 11

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, equipment qualifications are deficient in that acceptance criteria are not specified, and discrepancies are not documented. For example:

- a) The Re-Qualification of the [REDACTED] which was used in the production of Benztropine Mesylate Tablets, Batch # RBR-2137, does not have clearly defined acceptance criteria. In addition, there is no discrepancy report to explain why equipment drawings, equipment schematics, equipment manuals and purchase orders were not available; what steps had been taken in an attempt to obtain these materials and why this was acceptable.
- b) The specified utility requirements were not met in the equipment re-qualification for [REDACTED] which was used in the production of Benztropine Mesylate Tablets, Batch # RBR-2137. The specification for voltage was 220 Volts, but the actual voltage is 208 Volts. There is no discrepancy report to explain why this failure to meet the specification is or is not acceptable.
- c) There are no equipment qualifications for the [REDACTED] or the Blue M Drying Oven ID # 273. These ovens are used in the production of Benztropine Mesylate Tablets as well as more than fifteen other products.

Corrections:

All manufacturing and laboratory equipment/instruments have been reviewed for qualification. All equipment/instruments have been qualified. Review and remediation was conducted by third party consultants.

The Blue M Drying Ovens [REDACTED] have been assessed by [REDACTED] and have been qualified.

In reviewing the heat distribution studies for the dryers (which are expected to operate at 120 degrees F), it was noted that the acceptance criteria of [REDACTED] from the setpoint was designated as an acceptable tolerance for the read-out temperatures of the individual probes. I indicated that this meant that the chamber could range in temperature from [REDACTED]. Mr. Talbot explained that the tolerance should be tightened and noted that the actual results have been within approximately [REDACTED] of the setpoint. Mr. Talbot stated that the tolerance will be changed to [REDACTED] for all of the drying ovens.

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**OBSERVATION 12**

Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically, there is no assurance that preventative maintenance is conducted for equipment at scheduled intervals. For example:

- a) Duct tape was observed on the feed throat of Fitzmill #12 during the tour of manufacturing operations.
- b) There are no preventative maintenance programs for the Lydon Brothers Inc. Drying Oven ID # 271 or the Blue M Drying Oven ID # 273.
- c) Preventative Maintenance is to be conducted on Double Cone Blender ID # 41 every six months according to DOI # PRD-011: Blenders - Preventative Maintenance and Repairs." However, no maintenance had been conducted between 1/8/04 and 12/8/04 or between 5/12/05 and 5/19/06.

Corrections:

SOPs DOI 248: Drying Oven calibration, DOI 249: Drying Oven Preventative Maintenance and Repairs and DOI PRD 011: Blenders – Preventive Maintenance & Repairs provide procedures for preventative maintenance for the drying ovens and blenders. The duct tape was removed from the feed throat of the Fitzmill and is no longer used on any equipment. A maintenance mechanic has also been hired since the previous inspection.

In addition, the Calibration Manager computer system has been validated. This program has been fully operational since March 2007 and is used for the scheduling and documenting of calibration and preventative maintenance operations in both the laboratory and manufacturing.

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**MATERIALS SYSTEM**

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**OBSERVATION 13**

Rejected in-process materials are not identified and controlled under a quarantine system to prevent their use in manufacturing or processing operations for which they are unsuitable.

Specifically, rejected Batches are not labeled as rejected or placed in a section of the warehouse for rejected products. For example:

a)

[REDACTED] On 7/13/06, this Batch was not labeled as

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rejected and was in the WIP (work in progress) Warehouse, labeled as "In-Process".

- b) Cyclobenzaprine HCL Tablets, Batch 5846 was rejected on 10/7/05, when blend uniformity samples failed to meet specifications. On 7/13/06, this Batch was not labeled "rejected" and was found in the WIP (work in progress) warehouse, labeled as "In-Process".
- c) Dantrolene Sodium Capsules, Batches 60220A, 60228A and 60229A, were rejected on 5/17/06, when final blend uniformity samples failed to meet specifications. On 7/13/06, this Batch was not labeled as rejected when it was found in the in the WIP (work in progress) Warehouse.

**Corrections:**

Departmental Operating Instructions, DOI QA 002: Rejecting an Item, was updated to include timeframes for hold/rejection status and for placing the rejected stickers on the product. In addition, DOI PRD 255: Reject.Cage Operations to include directions on how to handle rejected materials.

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**OBSERVATION 14**

Written procedures are not followed for the receipt and storage of components.

Specifically, all locations are not identified throughout the warehouse as required by Departmental Operating Instructions (DOI) PRD-068: "Raw Material Locator System", nor are they recorded on Material Inventory Cards as required by DOI PRD-066: "Receiving Raw Materials & Packaging Components," to describe where materials are located in the warehouse. For example:

- a) Magnesium Hydroxide PO # 60875 was observed in the warehouse in an unidentified location. There was no location filled out on the Material Inventory Card.
- b) Unitab Microcrystalline Cellulose PO # 60134-6 was observed in the warehouse in an unidentified location. There was no location filled out on the Material Inventory Card.

**Corrections:**

All locations within the warehouse have been identified and locations are now recorded on the Material Inventory Cards. Retraining was given to operators regarding the revised SOPs: DOI WHS 001: Receiving Raw Materials and Packaging Components, DOI WHS 003: Raw Material Locator System and DOI WHS 005: Material Inventory Card.

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**OBSERVATION 15**

There was a failure to handle and store components at all times in a manner to prevent contamination.

Specifically, all raw materials for a Batch are weighed in the manufacturing room without cleaning between the dispensing of each ingredient. The cleaning log for the room only reflects the cleaning of the room after the production

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of the Batch. In addition, procedures do not indicate that the active ingredient should be the last material to be weighed.

**Corrections:**

DOI PRD247: Operating Instructions for Weighing Raw Materials to be Used in Pharmaceutical Production, was updated in order to state that inactive ingredients are to be weighed first, one at a time, active ingredients are to be weighed last and a dry cleaning is to take place between the dispensing of each ingredient. In addition, the new facility on 900 Riverview Drive, Totowa, NJ has specifically designated dispensing rooms for future production operations.

The following discussion item from the previous inspection was also verified as corrected during the current inspection.

***Labeling of glassware:***

During the tour of the analytical laboratory, I noted that all glassware on bench tops were clearly labeled and identified according to DOI: QC-157: Labeling of Standard/Sample Solution Vessels. This procedure had been presented prior to the close of the previous inspection.

An outline of corrective actions taken in response to the previous FDA 483 was provided by Ms. Wanda Eng and is attached as **Exhibit 30**.

**EXHIBITS COLLECTED**

- 1) Floor Plan, Little Falls, 1 page
- 2) Product List, 4 pages
- 3) Organizational Charts, 2 page
- 4) Position Descriptions, 12 pages
- 5) List of discontinued products, 1 page
- 6) Quality Systems Improvement plan, 7 pages
- 7) Flow diagram for Acetaminophen, Caffeine, and Dihydrocodeine Bitartrate Capsules, 1 page
- 8) OOS result 8/21/07, Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1 twelve-month stability test point, 4pages
- 9) Re-shaken flask results Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1 twelve-month stability test point, 4pages
- 10) Repeat Assay, new composite powder, Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1 twelve-month stability test point, 4pages

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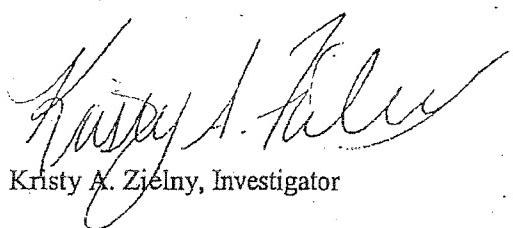
- 11) Repeat test, 2<sup>nd</sup> analyst, Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1 twelve-month stability test point, 4pages
- 12) Three additional bottles Lot 60484A1 pulled from stability, 2 pages
- 13) Field Alert Report Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484A1, 4 pages
- 14) Carisoprodol Aspirin and Codeine Phosphate Tablets, Lot # 60484AQ (500 count bottles) discontinued, 1 page
- 15) Lot # 60484AQ and Lot # 60484A1 stability summaries showing higher trend of salicylic acid results, 2 pages
- 16) Testing of retains, Carisoprodol Aspirin and Codeine Phosphate Tablets, 2 pages
- 17) Investigation Log No. 07-008 fro Quinipril Hydrochloride and Hydrochlorothiazide Tablets 20/12.5 mg Lot # 70111A, 11 pages
- 18) Investigation Log No. 07-009 for Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5/1.5 mg Lot # 70097A, 11 pages
- 19) Investigation Log No. 07-010 for Hydroxyzine Hydrochloride Tablets 10 mg. Lot # 70132A, 11 pages
- 20) Investigation 07-031, 8 pages
- 21) Investigation 07-037, 3 pages
- 22) "Investigation of Deviations" (SOP # 0033), 2 pages
- 23) "Investigation of Out of Specification Results" (DOI # QC-059), 2 pages
- 24) Hold Notification Form dated 9/6/07, Buspirone HCl Master Blend Lot 70683A, 1 page
- 25) Excerpt for batch record Buspirone HCl Master Blend Lot 70683A, 2 pages
- 26) Investigation for low yield of Carisoprodol, Aspirin and Codeine Phosphate Tablets USP 200/325/16mg, Lot 70488A and excerpt from batch record, 3 pages
- 27) Investigation of Deviation Report 07-003, 3 pages
- 28) Investigation of Deviation Report 07-004, 3 pages
- 29) Interim report for investigation 07-013, 4 pages
- 30) Outline of corrective actions taken in response to the previous FDA 483, 8 pages

#### ATTACHMENTS

- FDA 482, dated 9/5/07, 1 page  
FDA 483, dated 9/28/07, 3 pages  
Copy of [REDACTED]  
[REDACTED]  
Collection report for Profile Sample # 377413

Establishment Inspection Report  
Actavis Totowa LLC  
Little Falls, NJ 07424-5608

FEI: 2244683  
EI Start: 09/05/2007  
EI End: 09/28/2007



Kristy A. Zjelny

Kristy A. Zjelny, Investigator

RELEASE

REVIEWED BY AZ 5/7/08  
DATE